CME

American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease

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This guideline presents an update to the 2013 American College of Gastroenterology Guideline on the Diagnosis and Management of Celiac Disease with updated recommendations for the evaluation and management of patients with celiac disease (CD). CD is defined as a permanent immune-mediated response to gluten present in wheat, barley, and rye. CD has a wide spectrum of clinical manifestations that resemble a multisystemic disorder rather than an isolated intestinal disease, and is characterized by small bowel injury and the presence of specific antibodies. Detection of CD-specific antibodies (e.g., tissue transglutaminase) in the serum is very helpful for the initial screening of patients with suspicion of CD. Intestinal biopsy is required in most patients to confirm the diagnosis. A nonbiopsy strategy for the diagnosis of CD in selected children is suggested and discussed in detail. Current treatment for CD requires strict adherence to a gluten-free diet (GFD) and lifelong medical follow-up. Most patients have excellent clinical response to a GFD. Nonresponsive CD is defined by persistent or recurrent symptoms despite being on a GFD. These patients require a systematic workup to rule out specific conditions that may cause persistent or recurrent symptoms, especially unintentional gluten contamination. Refractory CD is a rare cause of nonresponsive CD often associated with poor prognosis.

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INTRODUCTION

Guiding principles

This document presents official recommendations from the American College of Gastroenterology (ACG) on the diagnosis, management, and follow-up of celiac disease (CD) in children and adults. This guideline was developed in compliance with the Institute of Medicine standards for practice guidelines and uses the Grading of Recommendation Assessment Development and Evaluation (GRADE) approach. The primary objective is to produce high-quality evidence-based clinical practice guidelines to answer common clinical questions and improve health care.

The guideline evaluates a broad spectrum of clinical practice, including indication for CD testing; diagnostic strategies for individuals on a gluten-containing diet or following a gluten-free diet (GFD); role of biopsy for confirmation of the diagnosis; indication for gluten challenge and genetic testing; general approach to management; preventive care such as vaccination; monitoring of GFD adherence including discussion of gluten detection devices, probiotics, goals of therapy, and outcomes; and the differential diagnosis for nonresponsive CD.

The guideline developers from ACG identified key questions that providers face frequently in the diagnosis, management, and follow-up of patients with CD (Tables 1 and 2). This guideline is intended for healthcare providers who care for patients with CD.

Background

This guideline presents an update to the 2013 ACG Guidelines: Diagnosis and Management of CD with updated recommendations for the evaluation and management of patients with CD (1). CD affects nearly 1% of residents of the United States (2). CD is defined as a permanent immune-mediated response to gluten present in wheat, barley, and rye (3). CD has a wide spectrum of clinical manifestations that resemble a multisystemic disorder rather than an isolated intestinal disease. CD is characterized by small bowel injury and the presence of specific antibodies. Detection of CD-specific antibodies (e.g., tissue transglutaminase [TTG]) in the serum is very helpful for the initial screening of patients with suspicion of CD. Intestinal biopsy is required in most patients to confirm the diagnosis. A nonbiopsy strategy for the diagnosis of CD in selected children is suggested and discussed in detail. Current treatment of CD requires strict adherence to a GFD and lifelong medical follow-up. Most patients have excellent clinical response to a GFD. Nonresponsive CD is defined by persistent or recurrent symptoms despite being on a GFD. These patients

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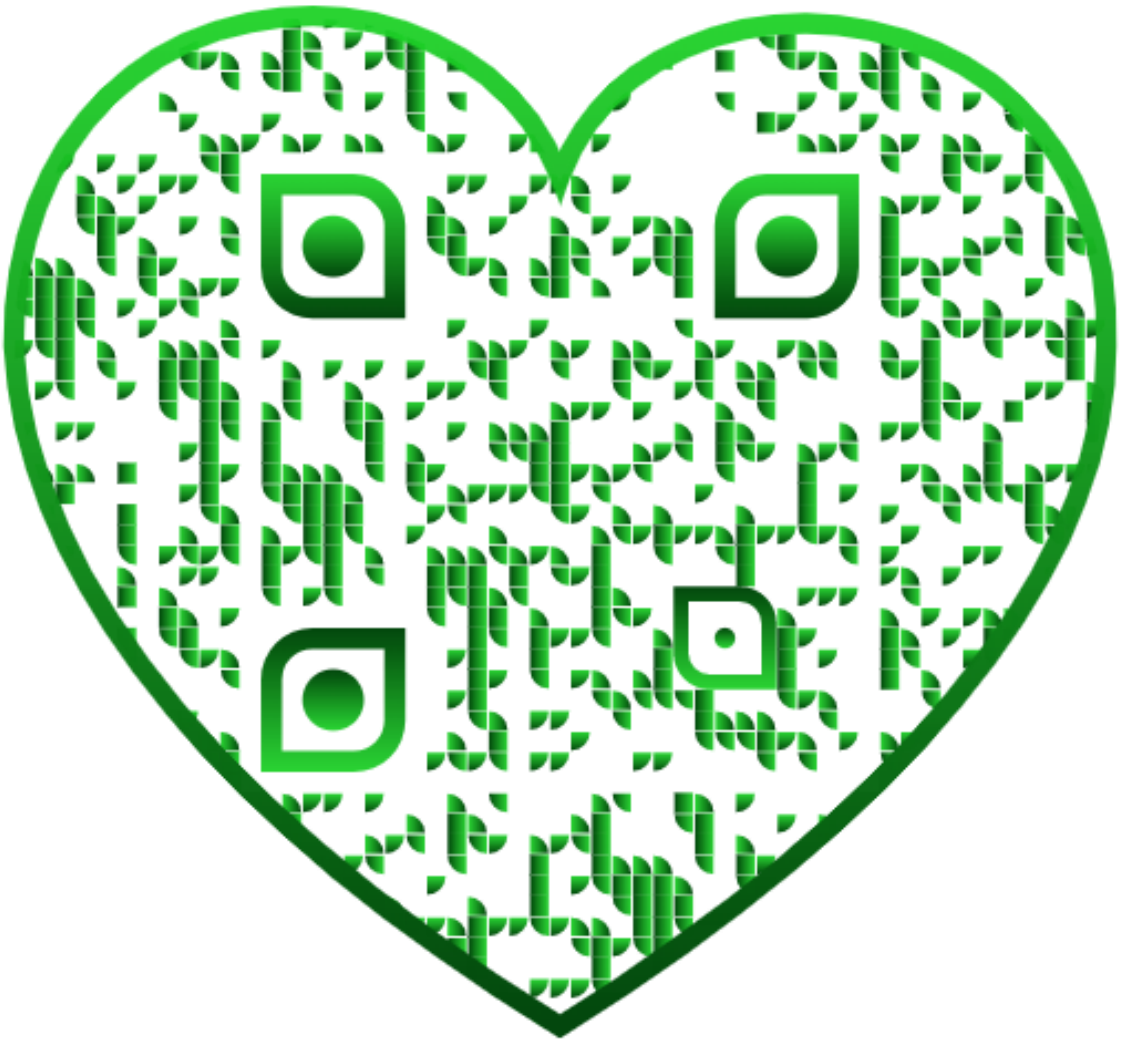

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Table 1. Questions and recommendations

Question/recommendation	Quality of evidence	Strength of recommendation	Dissent
1. Should a combination of noninvasive serology tests vs duodenal biopsy be used to confirm the diagnosis of CD in children and adults?			
A. We recommend EGD with multiple duodenal biopsies for confirmation of diagnosis in both children and adults with suspicion of CD	Moderate	Strong	1
B. We suggest a combination of high-level TTG IgA (>10× upper limit of normal) with a positive EMA in a second blood sample as reliable tests for diagnosis of CD in children. In symptomatic adults unwilling or unable to undergo upper GI endoscopy, the same criteria may be considered after the fact, as a diagnosis of likely CD.	Moderate	Conditional	0
2. Should intestinal mucosa healing vs clinical and serological remission be used as a goal of GFD therapy to improve long-term outcomes (5 yr or more) such as mortality, cancer risk, and osteoporosis in adults with CD?			
We suggest setting a goal of intestinal healing as an end-point of GFD therapy. We advocate for individualized discussion of goals of the GFD with the patient beyond clinical and serological remission.	Low	Conditional	0
3. Should gluten detection devices vs current standard of care be used to monitor adherence to GFD and/or patients' dietary decision-making?			
We suggest against routine use of gluten detection devices in food or biospecimens among patients with CD.	Low	Conditional	1
4. In patients with CD, what is the effect of probiotics in addition to GFD on the rates of clinical remission and mucosal healing compared with GFD alone?			
There is insufficient evidence to recommend for or against the use of probiotics for the treatment of CD.	Very low	Evidence gap	1
5. In patients with newly diagnosed CD, what is the effect of GFD without oats on increasing the rate of clinical remission and mucosal healing compared with GFD with oats?			
We recommend consumption of gluten-free oats in the diet of those with CD. Gluten contamination of oats, variable toxicity in different varieties of oats, and the small risk for an immune reaction to the oat protein avenin requires monitoring for oat tolerance.	Moderate	Strong	0
6. For patients with CD, does the use of pneumococcal vaccine reduce the future risk of serious pneumococcal infection compared with no pneumococcal vaccine?			
We suggest vaccination to prevent pneumococcal disease in patients with CD	Low	Conditional	0
7. Should case finding vs mass screening be used to improve detection of CD in the general population?			
A. We recommend case finding to increase detection of CD in clinical practice	Low	Strong	0
B. We recommend against mass screening for CD in the community	Low	Strong	0
8. Are TTG and DGP antibodies in combination more accurate in diagnosing CD in children younger than 2 yr compared with TTG alone?			
A. We recommend the immunoglobulin IgA anti-TTGA-IgA as the preferred single test for detection of CD in children younger than 2 yr who are not IgA deficient	Moderate	Strong	0
B. We recommend that testing for CD in children with IgA deficiency be performed using IgG-based antibodies (DGP-IgG or TTG-IgG)	Moderate	Strong	0

CD, celiac disease; DGP, deamidated gliadin peptide; EMA, endomysial antibody; GFD, gluten-free diet; TTG, tissue transglutaminase.

require a systematic workup to rule out specific conditions that may cause persistent or recurrent symptoms, especially unintentional gluten contamination. Refractory CD (RCD) is a rare cause of nonresponsive CD often associated with poor prognosis.

Epidemiology and burden of disease

CD is common, with a point prevalence around 1% in most populations (3). The incidence of CD diagnosis has risen in recent decades (4), and this rise has been attributed to both increased awareness and testing (5) as well as a rise in autoimmunity; the latter has been demonstrated by seroprevalence studies of apparently asymptomatic individuals (6,7). Although earlier studies found that most patients with CD remain undiagnosed (2,5), this seems to have shifted in recent years (8).

Measuring the burden of CD is limited by several factors, such as undiagnosed asymptomatic individuals and the fact that there are no prescription medications to treat the condition, which likely leads to undercoding. Although nearly 3 million Americans are estimated to have CD based on seroprevalence studies (2,5), an analysis of the National Ambulatory Medical Care Survey found only 190,381 office visits in 2014 associated with a diagnosis code indicating CD (9). At the same time, disease burden

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Table 2. Summary of Clinical Questions Evaluated using the PICO format

Question	Population	Intervention	Comparison	Outcome
1	Children and adults with CD	Duodenal biopsy	Serology tests	Diagnostic accuracy
2	Adults with CD	Mucosal healing	Clinical/serological remission	Mortality
3	Patient with CD	Use of gluten detection devices	Standard of care[a]	Improve adherence to GFD or help dietary decision making
4	Adults with CD	Probiotic + GFD	GFD alone	Clinical remission/mucosal healing
5	CD patients	Oats	No oats	Clinical remission/mucosal healing
6	Adults with CD	Pneumococcal vaccine	No pneumococcal vaccine	Serious pneumococcal infections
7	General population	Case finding	Mass screening	Rate of detection of CD
8	Children <2 yr old	TTG + deamidated peptide antibodies	TTG alone	Diagnostic accuracy

CD, celiac disease; GFD, gluten-free diet; PICO, patient/population/problem, intervention, comparison, outcome; TTG, tissue transglutaminase.
[a]Definition: regular follow-up without the use of gluten detection devices.

has been estimated as considerable based on economic analyses measuring the cost associated with outpatient care among patients diagnosed with CD (10). This has been found to be particularly increased in the first 2 years after diagnosis but has also increased in the years before diagnosis (11), presumably because of the development of symptoms that prompt investigation. In addition to the costs incurred by investigation of symptoms, diagnosis, and monitoring, the increased cost of gluten-free foods compared with their gluten-containing counterparts is an important component of disease burden (12). This cost is compounded by the noneconomic burden of the diet as reported by patients, whose rating of CD treatment burden is substantial (13).

Methods of guideline development

The process of guideline development is evidence-based, transparent, and systematic. Generation of recommendation involves both content and methodology experts. The content experts determined the key clinical questions using the population/patient/problem, intervention, comparison, outcome (PICO) format, identified related literature and provided content expertise for interpretation of evidence, and constructed the manuscript with key concepts and recommendations. Two experienced methodologists assessed the level of evidence using the GRADE framework and facilitated and guided discussion surrounding evidence and strength of recommendation. Technical remarks or key concepts are added to recommendations to help reconcile the level of the recommendation with the quality of the evidence and to facilitate implementation (Table 3).

GRADE SYSTEM

The strength of evidence is expressed as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (any estimate of effect is very uncertain). The strength of the recommendation is expressed as strong or weak (it is permissible to use "conditional" or "discretionary" in place of the term "weak").

The guidelines, in addition to grading strength of evidence and strength of recommendation, will allow for dissent from the majority opinion by one or more authors. This will simply be recorded by 0 dissent, 1 dissent, etc.

These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

Diagnosis

1. Should a combination of noninvasive serology tests vs duodenal biopsy be used to confirm the diagnosis of CD in children and adults?

Recommendations

1A. We recommend EGD with multiple duodenal biopsies for confirmation of diagnosis in both children and adults with suspicion of CD (strong recommendation, moderate quality of evidence; dissent 1).

1B. We suggest a combination of high-level TTG IgA (>10× upper limit of normal) with a positive endomysial antibody (EMA) in a second blood sample as reliable tests for diagnosis of CD in children. In symptomatic adults unwilling or unable to undergo upper GI endoscopy, the same criteria may be considered after the fact, as a diagnosis of likely CD (conditional recommendation, moderate quality of evidence; dissent 0).

Key concepts

1. Multiple biopsies of the duodenum (1 or 2 from bulb and 4 from distal duodenum) are necessary for diagnosis of CD.
2. EGD and duodenal biopsies can also be useful for the differential diagnosis of other malabsorptive disorders or enteropathies.
3. Lymphocytic duodenosis (≥25 intraepithelial lymphocytes per 100 epithelial cells) in the absence of villous atrophy is not specific for CD, and other causes should be considered.

Background

Intestinal biopsy has been a central test to confirm the diagnosis of CD since the late 1950s (14). Traditionally, the diagnosis of CD required 3 intestinal biopsies: a biopsy on a gluten-containing diet

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Table 3. Key concepts

Recommendation 1A and 1B
Multiple biopsies of the duodenum (1 or 2 from bulb and 4 from distal duodenum) are necessary for diagnosis of CD
EGD and duodenal biopsies can also be useful for the differential diagnosis of other malabsorptive disorders or enteropathies.
Lymphocytic duodenosis (≥25 intraepithelial lymphocytes per 100 epithelial cells) in the absence of villous atrophy is not specific for CD, and other causes should be considered
Recommendation 2
Upper endoscopy with intestinal biopsies is helpful for monitoring in cases with a lack of clinical response or relapse of symptoms despite a GFD
Follow-up biopsy could be considered for the assessment of mucosal healing in adults in the absence of symptoms after 2 yr of starting a GFD after shared decision-making between patient and provider
Recommendation 3
The standard of care in assessing diet adherence involves an interview with a dietitian with expertise in the GFD
Technologies to qualitatively detect gluten in food or biospecimens may not distinguish between clinically significant and trivial gluten exposure
There is a paucity of evidence to suggest that using gluten detection technology enhances diet adherence or quality of life.
Studies are needed to evaluate the utility of gluten detection technologies to improve GFD adherence and clinical outcomes in CD.
Recommendation 4
Dysbiosis is a feature of CD, but its role in disease pathogenesis and symptomatology is uncertain.
Despite the widespread use of probiotics, a benefit in the management of CD is not established.
Recommendation 5
Oat consumption seems to be safe for most individuals with CD, but may be immunogenic in a subset of patients.
Heterogeneity in the tolerance of oats may be related to differences in the origin/harvesting and quantity of oats consumed.
Intervals for monitoring symptoms and serology after gluten-free oats are introduced into the diet are not known.
Recommendation 6
Vaccination against pneumococcal infection is safe and effective.
Vaccination is widely recommended for all adults older than 65 yr and smokers aged 19–64 yr or adults with certain underlying conditions.
Recommendations 7A and 7B
Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, abdominal pain, and bloating, should be tested for CD.
Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD.
Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs, symptoms or laboratory evidence of CD.
Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD.
Recommendations 8A and 8B
TTG-IgA and EMA-IgA are reported to be less accurate in children younger than 2 yr.
Current guidelines recommend that testing for CD in children younger than 2 yr include both TTG-IgA and DGP-IgG.

CD, celiac disease; DGP, deamidated gliadin peptide; EGD, esophagogastroduodenoscopy; EMA, endomysium antibodies; GFD, gluten-free diet; TTG, tissue transglutaminase.

(diagnosis), a biopsy after a period on GFD (to demonstrate improvement), and a biopsy after a gluten challenge (to demonstrate worsening) (15). Later studies demonstrated that a biopsy at the time of diagnosis in children without additional intestinal biopsies was able to correctly diagnose 95% of cases (16). Thus, intestinal biopsy for confirmation of the diagnosis became standard of care. More recently, in view of the excellent specificity of TTG antibodies at high titters, a nonbiopsy diagnosis for selected children with suspicion of CD has been proposed (17).

Evidence and rationale

The availability of CD-specific serological tests facilitated the recognition of patients with CD and the wide spectrum of clinical manifestations (6,18). A positive serological test is supportive of the diagnosis but no single test is 100% specific for CD, and the diagnostic accuracy varies considerably between laboratories (19). Indeed, a large international study found that laboratory sensitivity ranged from 63% to 93%, and specificity ranged from 96% to 100% when comparing TTG assays among various research and clinical laboratories (20). Serological tests may perform less well in the clinical setting than research (a positive result of both TTG and EMA antibodies had a sensitivity of 81% in 1 study) (21). A diagnosis of CD is definitively confirmed by the demonstration of histological changes associated with the disease as classified according to Marsh or more recently the simplified Corazza classification (22,23) (see Supplementary

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Table 1, http://links.lww.com/AJG/C755). Small bowel biopsy is also useful for the differential diagnosis of other enteropathies or malabsorptive disorders (24–27).

The diagnostic approach to CD for adults incorporates serologic and histologic data and has not changed since the publication of the last version of the ACG Guidelines (1). Testing should be considered in patients with signs or symptoms suggestive of CD, including diarrhea, weight loss, abdominal pain and bloating, or laboratory abnormalities such as unexplained elevated serum aminotransferase levels. Testing of asymptomatic individuals in populations at higher risk of CD can be considered (see Section 8).

Serologic testing for CD should consist of measuring TTG IgA while on a regular (gluten-containing) diet and, if the patient has not previously been tested for IgA deficiency, concurrent measurement of total IgA (Figure 1). Patients with an elevated TTG IgA level should proceed to EGD with duodenal biopsy. Some patients undergo EGD for the investigation of gastrointestinal symptoms before serology testing with either endoscopic findings of CD leading to duodenal biopsies or routine duodenal biopsies with a subsequent finding of villous atrophy. In these patients, checking a TTG IgA level is recommended to support the diagnosis of CD before starting a GFD. A negative TTG IgA in patients without IgA deficiency has a high negative predictive value if the pretest probability is low or moderate (19), and CD can be considered adequately ruled out in this scenario. In patients with high pretest probability, EGD with duodenal biopsy should be considered even with a negative serology. If IgA deficiency is present, then an IgG serology (commonly deamidated gliadin peptide [DGP] and/or TTG) should be measured.

The role of DGP IgG testing in IgA-deficient patients with negative TTG IgG remains uncertain. Although a small proportion of patients with CD have isolated elevations of this antibody (28), the low positive predictive value has precluded its inclusion into diagnostic algorithms. Despite consistent reports of high specificity of EMA (19), given the limited availability and operator dependence of this assay, it is not included in the diagnostic algorithm for CD evaluation, outside of its use as a confirmatory test in children candidates for a nonbiopsy diagnostic algorithm (17).

This algorithm (Figure 1), previously applicable to adults and children ≥2 years, can now be applied to adults and children at any age, as long as the individual undergoing testing is maintaining a regular (gluten-containing) diet. Special considerations for individuals following a GFD are also highlighted in the figure (for further explication of serologic testing in pediatric populations, see Section 9).

Symptomatic patients whose pretest suspicion for CD is high (>5%) should undergo upper gastrointestinal endoscopy with duodenal biopsy irrespective of serologic results, given the imperfect sensitivity of serology, risk of verification bias on studies assessing CD testing, the possibility of seronegative CD, and differential diagnosis with other enteropathies (25,29).

Genetic testing for CD-compatible human leukocyte antigen (HLA) haplotype is not required for diagnosis in all cases but may be helpful in selected situations such as in the context of serology-histology discrepancy (1,3,25). If negative, CD is ruled out. HLA testing is also central to the approach to CD testing for individuals

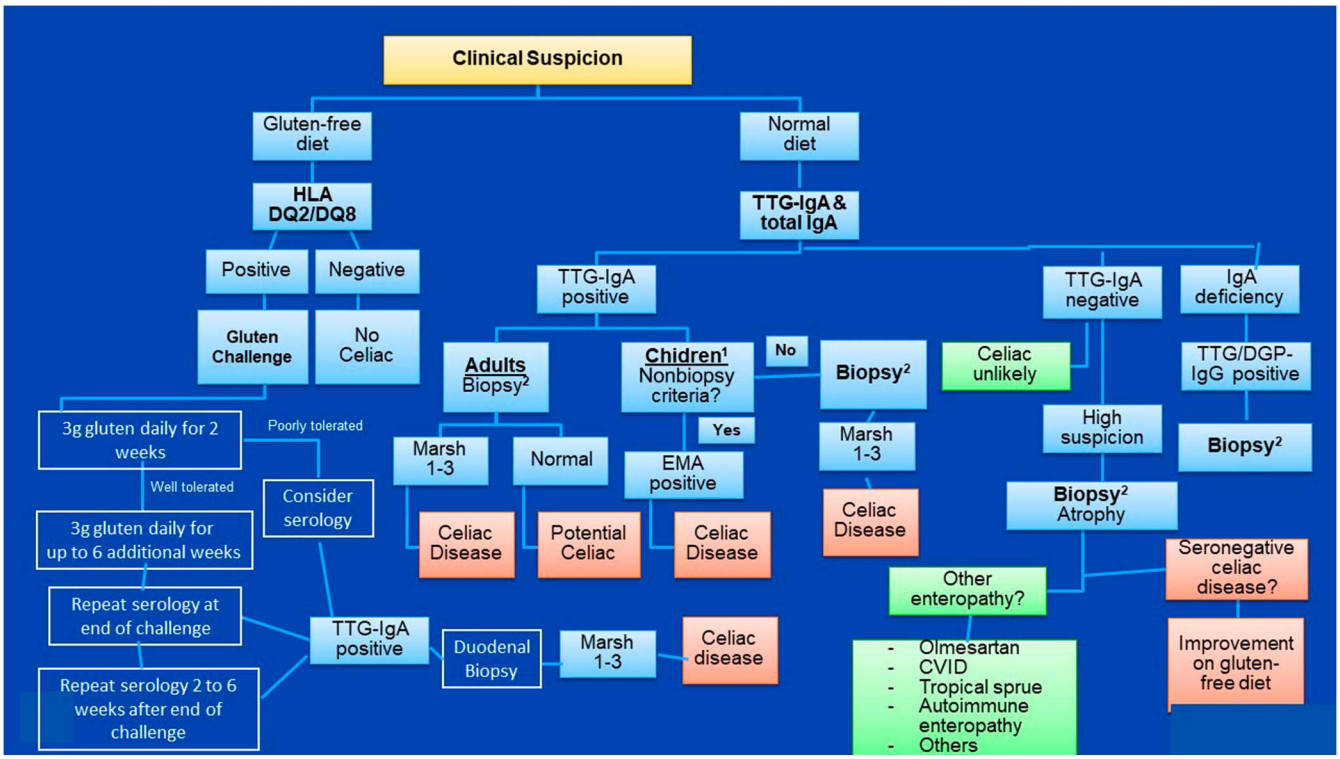

Figure 1. CD diagnostic testing algorithm. (**1**) Nonbiopsy criteria in children requires high-level TTG IgA (>10× upper limit of normal) with a positive EMA in a second blood sample in children only if family agrees with no-biopsy strategy. (**2**) Duodenum sampling recommended: 1 or 2 biopsies from bulb and 4 biopsies from distal duodenum. CD, celiac disease; CVID, common variable immune deficiency; DGP, deamidated gliadin peptide; EMA, endomysial antibody; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; TTGA, tissue transglutaminase antibody.

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who have already started a GFD before evaluation; in the presence of a CD-compatible haplotype, a gluten challenge can be offered.

Histological abnormalities associated with CD can be patchy (30). Multiple biopsies of duodenum should be performed if the diagnosis of CD is considered, irrespective of the clinical presentation. Among 132,352 patients without known CD who underwent duodenal biopsy in the United States, the probability of a new diagnosis of CD was significantly increased when ≥4 specimens were submitted (1.8% vs 0.7%, $P < 0.0001$) as compared with less than 4 (31). Unfortunately, 4 or more biopsies were obtained in only 39% of patients who underwent biopsy because of clinical suspicion of CD (31). In 1 study, the rate of duodenal biopsy was significantly lower among Black, older (≥70 years), and male patients (32). In children and adults with positive CD-specific serology, adding biopsies of the duodenal bulb increases the diagnostic yield of CD (e.g., 9%–13% had villous atrophy in the bulb alone) (33). In 1 study, a targeted duodenal bulb biopsy from either the 9-o'clock or 12-o'clock position in addition to biopsies of distal duodenum had a sensitivity of 96% for the diagnosis of CD (34). Care must be taken when interpreting duodenal bulb biopsies to allow for the normal surface architectural changes that overlie Brunner glands and the acute inflammatory changes of peptic duodenitis. It has been recommended by expert opinion that only a single biopsy specimen should be obtained with each pass of the biopsy forceps (35), based on the notion that specimen orientation may be improved (36). We recommend multiple biopsies of the duodenum including 1 or 2 specimens from the bulb (either 9-o'clock or 12-o'clock position) and at least 4 biopsies of postbulbar duodenum.

Lymphocytic infiltration (≥25 intraepithelial lymphocytes per 100 epithelial cells) also known as lymphocytic duodenosis is common in the general population (prevalence of 5.4%) and may be rising (37,38). Most patients with lymphocytic duodenosis do not belong to the spectrum of CD; however, workup to rule out CD is indicated (39,40). The frequency of diarrhea and weight loss was similar among patients with lymphocytic duodenosis and those with CD (40). Anemia, skin disorders, positive TTG, and HLA DQ2 were more frequent among patients with CD (40). Other disorders have been associated with lymphocytic duodenosis including *Helicobacter pylori* infection, medications (e.g., nonsteroidal anti-inflammatory drugs), small bowel bacterial overgrowth, nonceliac wheat/gluten sensitivity, and systemic autoimmune disorders. Persistent intraepithelial lymphocytosis was observed in 56% patients with treated CD despite the evidence of normal villous architecture, and the only factor associated with this finding was oat consumption (41). Among 56 children without a prior diagnosis of CD and lymphocytic duodenosis evaluated at a referral center, CD was diagnosed in only 9% of these cases (42). A GFD may be considered in symptomatic children and adults with either lymphocytic duodenosis or Marsh II (lymphocytic duodenosis and crypt hyperplasia without atrophy) lesions who have elevated CD-related antibodies, especially EMA (43).

A guideline endorsed by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) proposed that it may be possible to avoid any intestinal biopsy in children who meet the following criteria: characteristic symptoms of CD, and TTG IgA levels >10× upper limit of normal (confirmed with a positive EMA antibody in a different blood sample) (17). This is based on prospective data in children (and, to a lesser degree, adults) (44–47). This nonbiopsy approach in symptomatic children has been adopted in Europe since 2012 and updated ESPGHAN guidelines in 2020 proposed that (i) HLA testing is no longer necessary and (ii) a biopsy-free approach for asymptomatic children (using the same criteria) is conditionally recommended (17). A nonbiopsy diagnosis requires that the family agrees with this approach. Given the high positive predictive value of serology and the European experience of a biopsy-free approach for symptomatic children, this approach is a reasonable alternative to the standard approach to a CD diagnosis in selected children. One limitation of this approach includes the absence of standardization of TTG assays and the real risk of misdiagnosis without following the strict criteria proposed by ESPGHAN in clinical practice. In addition, the use of a predefined threshold to select a population to avoid intestinal biopsy may not be the optimal strategy, although emerging evidence suggests that a nonbiopsy diagnosis may be accurate with different commercial serology kits and pretest probabilities (44,48,49). Unfortunately, solid information about nonbiopsy diagnosis of CD in the United States is not available yet.

The primary concern about advocating a nonbiopsy approach for adults is the relative paucity of data regarding the positive predictive value of serology in adults, as compared with the more extensive body of literature in children. One multicenter international study of adults found that a ≥10-fold elevation of TTG IgA had a positive predictive value of 95% for CD (50). Given the life-long treatment implications of a GFD, this may be unacceptably low. However, physicians may encounter clinical scenarios where a biopsy diagnosis may not be practical, such as a patient for whom an endoscopy and/or biopsy poses a cardiovascular or bleeding risk. Moreover, some patients with highly elevated serology may have already started a GFD before gastroenterology referral; among those who report a severe symptomatic response to gluten exposure, a gluten challenge followed by biopsy may not be advisable. As such, an "after-the-fact" diagnosis of likely CD can be given to symptomatic adult patients with a ≥10-fold elevation of TTG IgA (a second confirmatory test such as EMA antibody is also advisable in adults). This diagnosis of likely CD may be useful in research studies, including clinical trials for nondietary therapies, and, when considering candidacy for the prescription of such therapies, should they be approved. Other potential benefits of nonbiopsy diagnosis in adults include reduction in the healthcare cost, avoidance of discomfort, and time lost from work for EGD.

Future research

- Is there an optimal cutoff for serologic values that provides an acceptable positive predictive value for the diagnosis of CD in adults across a range of commercial laboratories?
- Does the positive predictive value of serologies vary according to the patient's symptomatology and the coexistence of other autoimmune diseases?
- What are the downstream effects in clinical practice of offering a nonbiopsy diagnosis strategy?
- Does a nonbiopsy diagnosis have an effect on adherence to the GFD?

Diet and long-term outcomes

2. Should intestinal mucosa healing vs clinical and serological remission be used as a goal of GFD therapy to improve long-term outcomes (5 years or more) such as mortality, cancer risk, and osteoporosis in adults with CD?

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Recommendation

2. We suggest setting a goal of intestinal healing as an end point of GFD therapy. We advocate for individualized discussion of goals of the GFD with the patient beyond clinical and serological remission (conditional recommendation, low quality of evidence; dissent 0).

Key concepts

1. Upper endoscopy with intestinal biopsies is helpful for monitoring in cases with a lack of clinical response or relapse of symptoms despite a GFD.
2. Follow-up biopsy could be considered for assessment of mucosal healing in adults in the absence of symptoms after 2 years of starting a GFD after shared decision-making between patient and provider.

Background

A GFD is the only effective therapy for CD (51). There are multiple benefits of strict adherence to the GFD (52). It is expected that symptoms improve within days of strict adherence to a GFD (e.g., diarrhea improved in most patients [80%] within 60 days) (53). Adherence to GFD is very effective in controlling a wide variety of symptoms and also reducing healthcare utilization (54). Experts consistently agree on the necessity of long-term monitoring of patients with CD. The number of patients with CD who receive follow-up is unknown. In the United States, follow-up seems to be suboptimal in practice (55). A systematic review supports the role of strict adherence to the GFD to control symptoms, improve quality of life, and decrease the risk of complications (56). Normal growth and development are achievable on a GFD and should be goals for monitoring children with CD. Control of symptoms (if present), facilitation of adherence to GFD, preventive care (e.g., vaccines, dual-energy x-ray absorptiometry [DXA]), monitoring of seroconversion (e.g., going from positive to negative serology), active surveillance of comorbidity (especially coexistent autoimmune disease), and avoidance or early detection of complications should be the general goals of monitoring after diagnosis of CD. Clinical follow-up after diagnosis may require multiple visits during the first year after diagnosis (e.g., 3, 6, 12 months) and regular visits (e.g., twice a year or yearly) thereafter (Figure 2). A visit with a dietitian after diagnosis is mandatory, and subsequent visits as needed to reinforce GFD education and adherence should be encouraged. Although the rate of mucosal healing after adoption of a GFD is variable (57), there is no question that this goal may be achievable over time, especially with good adherence to the GFD. However, the long-term benefit of active monitoring for mucosal healing after starting a GFD is controversial (58). In addition, there is poor correlation between serology and mucosal healing, and although a negative celiac serology (seroconversion) increases the probability of mucosal healing, correlation is not good enough and currently a repeat intestinal biopsy is the only reliable method to assess for mucosal healing (57).

Evidence and rationale

Intestinal biopsies are the only way to document mucosal healing of the intestine. Mucosal healing in CD after starting a GFD takes time and is incomplete or absent in a substantial number of patients diagnosed during adult life. Indeed, in adults, the intestine

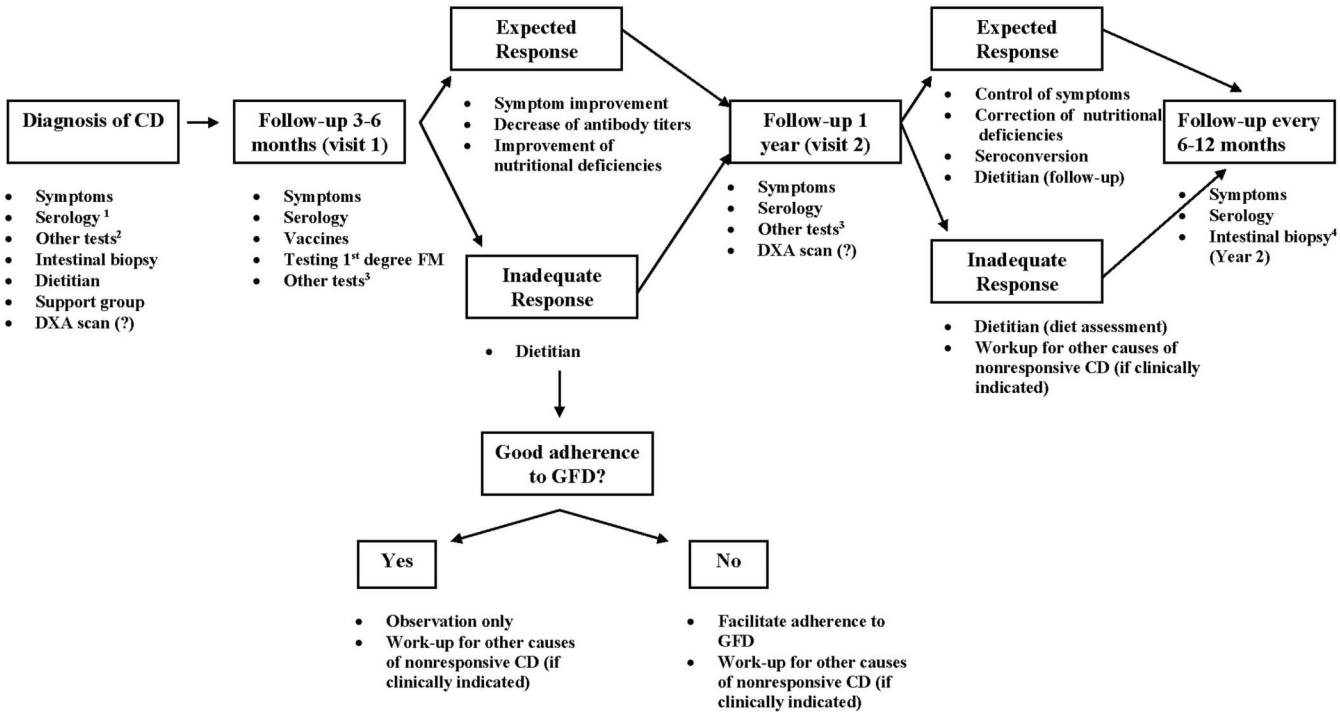

Figure 2. An approach to monitoring CD. (**1**) TTG and DGP can be used for monitoring CD considering the availability of test at baseline before initiation of the GFD. (**2**) Other tests may include complete blood count, alanine aminotransferase, aspartate aminotransferase, vitamins (A, D, E, B12), copper, zinc, folic acid, ferritin, and iron. (**3**) Blood tests at follow-up should be individualized to verify correction of laboratory tests that were abnormal at baseline. (**4**) The role of biopsy for monitoring CD and to check for mucosal healing (suggested at year 2 following the GFD) is discussed in detail in the text. CD, celiac disease; DGP, deamidated gliadin peptide; DXA, dual-energy x-ray absorptiometry; GFD, gluten-free diet; TTG, tissue transglutaminase.

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will often fail to heal despite negative serology and the absence of symptoms on a GFD (57). This lack of mucosal healing may be associated with increased risk of lymphoproliferative malignancy (hazard ratio [HR] = 2.81, 95% confidence interval [CI]: 2.10–3.67) (59), bone disease specifically increased hip fracture risk (HR = 1.67; 95% CI: 1.05–2.66) (60), and ultimately a diagnosis of RCD in symptomatic patients with good adherence to the GFD. A large Swedish study demonstrated a null risk of lymphoma (HR = 0.97; 95% CI = 0.44–2.14) among patients with normal follow-up histology, suggesting that mucosal healing could be a goal to consider during follow-up (61). Among a group of 381 patients with baseline and follow-up biopsy after GFD, mucosal healing was associated with a borderline lower risk of death (HR = 0.13, 95% CI: 0.02–1.06, P = 0.06) adjusted for age and sex (57). A much larger study from Sweden failed to confirm a protective role of mucosal healing on mortality risk, yet mortality risk was significantly lower among patients who underwent follow-up biopsy regardless of the result, compared with those who did not undergo a follow-up biopsy likely related to the benefits of regular medical follow-up (62). Moreover, mucosal healing does not influence the risk of serious infection (HR = 0.99, 95% CI: 0.88–1.11) (63), ischemic heart disease or atrial fibrillation (64), or adverse outcomes of pregnancy such as intrauterine growth retardation, low birth weight, preterm birth, or cesarean section (65). The putative benefits of follow-up biopsy are based on observational studies, and there are no prospective randomized trials of a follow-up biopsy approach vs a no-follow-up biopsy approach. Therefore, a personalized approach is required to decide monitoring of mucosal healing with shared decision-making between the physician and the patient.

In a US study, the median time from the onset of GFD to achieve mucosal healing in adults was 3 years (57). Accordingly, it is reasonable to consider a follow-up biopsy in adults after 2 years of starting a GFD to assess for mucosal healing. Mucosal healing was observed in 95% children within 2 years of starting a GFD (66). The consideration to perform follow-up biopsy may be different in children because they have higher rates of mucosal healing on a GFD, and there are additional inherent challenges for endoscopy in children that alter the risk-benefit ratio of this procedure. Currently, follow-up biopsy in asymptomatic children following a GFD is not recommended.

Future research

- Does a strategy of follow-up biopsy in asymptomatic individuals with CD have an effect on adherence to the GFD and quality of life?
- Are there biomarkers (used alone or in combination) that can predict the presence of mucosal healing vs persistent villous atrophy in treated CD?

Medical device use

3. Should gluten detection devices vs current standard of care be used to monitor adherence to GFD and/or patients' dietary decision-making?

Recommendation

3. We suggest against routine use of gluten detection devices in food or biospecimens among patients with CD (conditional recommendation, low quality of evidence; dissent 1).

Key concepts

1. The standard of care in assessing diet adherence involves interview with a dietitian with expertise in GFD.
2. Technologies to qualitatively detect gluten in food or biospecimens may not distinguish between clinically significant and trivial gluten exposure.
3. There is a paucity of evidence to suggest that using gluten detection technology enhances diet adherence or quality of life.
4. Studies are needed to evaluate the utility of gluten detection technologies to improve GFD adherence and clinical outcomes in CD.

Background

In recent years, multiple commercially available tools have been introduced that detect gluten in food and biospecimens. These measure gluten proteins, but because they do not directly diagnose or treat a medical condition, they are not subject to US Food and Drug Administration oversight. Evidence of their performance characteristics has been published in the peer-reviewed literature, and these tools are directly marketed to the public.

Evidence and rationale

The concept of patient-directed testing for gluten dates back to 1991 (67) and subsequent commercially available kits largely for home use (Glutentox and EZ gluten) were developed (68,69). More recently, the Nima sensor is a portable lateral flow gluten-sensor device that returns a "gluten found" or a "gluten-free" result for a pea-sized sample after approximately 3 minutes (70,71). The sensitivity of Nima for gluten depends on concentration and is >98% for food items >40 parts per million (ppm). However, this sensitivity does not take into account the limitation that Nima is unable to detect gluten in fermented form (e.g., in soy sauce or as barley malt). Although purely gluten-free foods correctly tested negative with the device >94% of the time, when foods were "spiked" with gluten that did not meet the threshold for 20 ppm (and are thus still considered gluten-free), the device returned a "gluten found" more than 50% of the time for items with 10–19 ppm of gluten. Therefore, both false-positive and false-negative results are a significant limitation. To date, there has been one published study measuring outcomes of patients using the Nima sensor. That study, a 30-subject pilot trial, found that adults (but not teenagers) given the Nima sensor reported improved CD-related quality of life after 3 months. Limitations of that study include the lack of a control arm of standard of care (or a sham device) and the lack of objective outcomes including villous histology. (72).

As other food-testing devices become available for people with CD (73–75), it is imperative that their validity be rigorously tested and their impact on patient outcomes be studied. Even if performance characteristics improve, such as superior ability to discern at the 20 ppm cutoff, there will be residual concern that sampling at the point of care (without homogenization) will be limited by the

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possible presence of gluten in an unsampled fragment of food. Thus, although this technology may prove useful for patients in select scenarios, the optimal setting and ultimate value of point-of-care gluten detection remains uncertain.

Because gluten is incompletely digested into peptide fragments by all individuals, these fragments are detectable in stool and urine, allowing for potential diagnostic use (76). Gluten fragments have been detected in stool up to 4 days after ingestion (77) and in urine for up to 2 days (78). Gluten in stool has been detected in nearly 30% of individuals with CD attempting to adhere to a GFD, and their presence may be more sensitive than a dietary questionnaire or TTG antibodies in identifying gluten exposure (79). The presence of urinary gluten fragments is a stronger predictor of persistent villous atrophy on follow-up biopsy than elevated serology (78).

Despite the potential promise of this technology, strategies of incorporating biospecimen detection of gluten into clinical management have not been tested. Although there may be a role for spot-checking for gluten exposure in select scenarios, it is not given that this approach will improve adherence to the GFD, quality of life, or other clinical outcomes. Furthermore, the clinical significance of these highly sensitive tests is uncertain. Urine testing can detect as little as 25 mg of ingested gluten, which may be below the limit of toxicity for a substantial proportion of patients with CD (78). Patients with persistent symptoms were actually less likely to have detectable gluten fragments compared with asymptomatic patients, possibly because of the fact that persistent symptoms (which are not necessarily due to gluten exposure) may spur further stringent efforts to avoid cross-contact with gluten (80). Because the patient perspective was not evaluated during guideline development, we recognize that there may be subgroups of patients with CD who find this type of novel technology valuable and believe it may give them a better sense of control over their disease. In the absence of certainty regarding whether to incorporate gluten detection technology in the management of CD, the evaluation of persistent or recurrent symptoms should take into account previously identified etiologies (81). This includes reviewing and confirming the initial diagnosis of CD, evaluation for inadvertent gluten exposure (through assessment by an expert dietitian and serology), assessment for a coexisting functional disorder, and selective testing (based on clinical suspicion) of food intolerances (e.g. lactose, fructose), pancreatic insufficiency, microscopic colitis, and small intestinal bacterial overgrowth, among others (82) (Figure 3).

RCD refers to ongoing symptoms and/or signs of malabsorption with intestinal villus atrophy despite the evidence of strict adherence to a GFD for at least 12 months (83). This is relatively rare outside of referral centers, comprising $<1\%$ of patients with CD (84). Central to the initial assessment is the differentiation between RCD types 1 and 2 by assessment for immunostains (CD3 and CD8), T-cell clonality through T-cell receptor polymerase chain reaction (PCR), and/or flow cytometric analysis of duodenal biopsy specimens. RCD type 1, characterized by a polyclonal T-cell population, likely has a heterogeneous group of etiologies, including inadvertent gluten exposure; as such, it may be managed with further dietary restriction, eliminating nearly all processed foods for a defined period (85). Medications that have been used to treat RCD include open-capsule budesonide, prednisone, immunomodulators, mesalamine, and biologics, although placebo-controlled data are lacking (83). RCD type 2, characterized by a clonal T-cell population, has a poorer prognosis and is often a precursor to enteropathy-associated T-cell lymphoma (86). Open-capsule budesonide, cladribine, and autologous stem-cell transplantation are potential therapeutic options. Parenteral nutritional support is often needed (83).

Future research

- What is the impact of the prescription of gluten detection technology on adherence to the GFD, symptom control, and mucosal healing?
- What is the optimal dietary counseling approach to patients who adopt gluten detection technology?
- Does the presence of gluten in food or stool and urine in quantities below traditionally regarded toxic doses result in clinically relevant outcomes?

Probiotics

4. In patients with CD, what is the effect of probiotics in addition to GFD on the rates of clinical remission and mucosal healing compared with GFD alone?

Recommendation

4. There is insufficient evidence to recommend for or against the use of probiotics for the treatment of CD (evidence gap in recommendation; very low quality of evidence; dissent 0).

Key concepts

1. Dysbiosis is a feature of CD, but its role in disease pathogenesis and symptomatology is uncertain.
2. Despite the widespread use of probiotics, a benefit in the management of CD is not established.

Background

Advances in our understanding of the intestinal microbiome have led to great interest among patients about the potential to translate these advances into therapeutic strategies for gastrointestinal conditions. Probiotics, live microorganisms administered for therapeutic purposes, have been evaluated extensively in conditions such as *Clostridioides difficile colitis* (87) and antibiotic-associated diarrhea (88) in which there is a suggestion of a beneficial effect. By contrast, far fewer data exist regarding the use of probiotics for the treatment of CD.

Evidence and rationale

The rationale for the use of probiotics stems from study findings that a state of dysbiosis exists in the duodenal microbiome of individuals with CD before and subsequent to the disease development. Infants with a family history of CD who carry the HLA DQ2 haplotype have higher proportions of certain gut microbial phyla (*Firmicutes* and *Proteobacteria*) compared with infants at low genetic risk (89). After diagnosis of CD and treatment with a GFD, the feces of children on this diet have lower counts of *Lactobacillus* species (90). Patients with ongoing gastrointestinal symptoms despite healed villi may have a distinct

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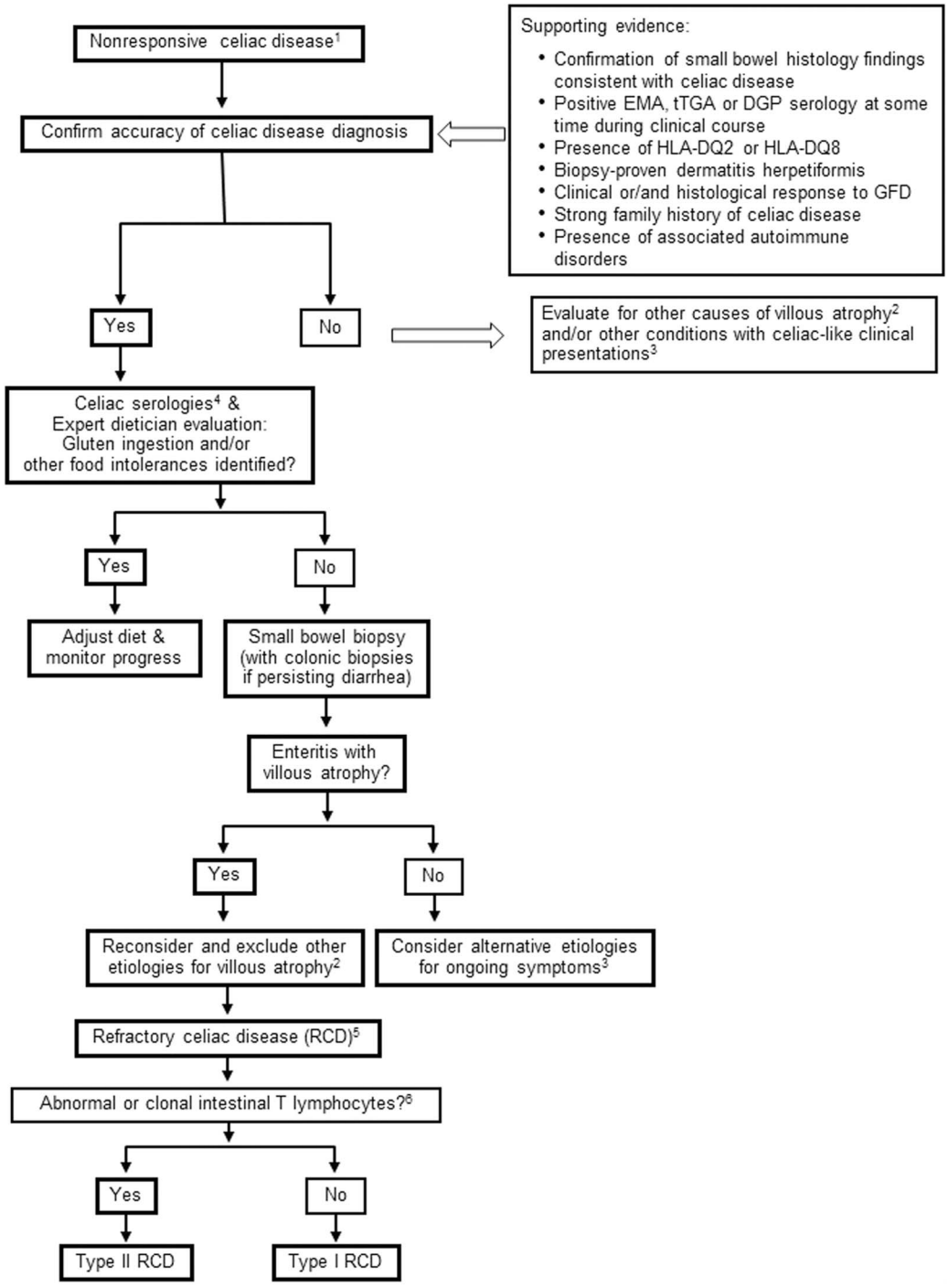
Nonresponsive celiac disease[1]
Confirm accuracy of celiac disease diagnosis
Supporting evidence:
• Confirmation of small bowel histology findings consistent with celiac disease
• Positive EMA, tTGA or DGP serology at some time during clinical course
• Presence of HLA-DQ2 or HLA-DQ8
• Biopsy-proven dermatitis herpetiformis
• Clinical or/and histological response to GFD
• Strong family history of celiac disease
• Presence of associated autoimmune disorders
Yes
No
Evaluate for other causes of villous atrophy[2] and/or other conditions with celiac-like clinical presentations[3]
Celiac serologies[4] & Expert dietician evaluation: Gluten ingestion and/or other food intolerances identified?
Yes
No
Adjust diet & monitor progress
Small bowel biopsy (with colonic biopsies if persisting diarrhea)
Enteritis with villous atrophy?
Yes
No
Reconsider and exclude other etiologies for villous atrophy[2]
Consider alternative etiologies for ongoing symptoms[3]
Refractory celiac disease (RCD)[5]
Abnormal or clonal intestinal T lymphocytes?[6]
Yes
No
Type II RCD
Type I RCD

Figure 3. An approach to the investigation of nonresponsive celiac disease (NRCD) and refractory celiac disease (RCD) (adapted from references Leffler et al. (81) Rubio-Tapia et al. (82)). (**1**) NRCD may be defined as persistent symptoms, signs, or laboratory abnormalities typical of CD despite 6–12 months of dietary gluten avoidance. (**2**) Causes of nonceliac, small-intestinal villous atrophy that may be misdiagnosed as CD include autoimmune enteropathy, tropical sprue, small-intestinal bacterial overgrowth, hypogammaglobulinemia and combined variable immunodeficiency, collagenous sprue, eosinophilic enteritis, Crohn's disease, and peptic duodenitis. (**3**) Conditions that present clinically in a similar fashion to CD but where villous atrophy is not evident include irritable bowel syndrome, food intolerances, small-intestinal bacterial overgrowth, eosinophilic enteritis, Crohn's disease, and microscopic colitis. (**4**) Positive celiac serologies despite 12 months of treatment with a GFD suggest that there may be ongoing gluten ingestion. (**5**) RCD may be defined as persistent or recurrent malabsorptive symptoms and signs with small-intestinal villous atrophy despite a strict GFD for more than 12 months and in the absence of other disorders, including overt lymphoma. (**6**) Abnormal intestinal lymphocytes may be identified by the immunohistochemistry of IELs or by flow cytometry showing an increased number of CD3-positive cells lacking CD8, or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis. CD, celiac disease; DGP, deamidated gliadin peptide; EMA, endomysium antibodies; GFD, gluten-free diet; HLA, human leukocyte antigen; IELs, intraepithelial lymphocytes; TTGA, tissue transglutaminase antibody.

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microbial signature in the duodenum compared with those whose symptoms have resolved (91,92).

Administration of probiotics might restore the putative dysbiosis documented in CD. A pilot study of 40 children with CD administered a probiotic containing a combination of Bifidobacterium strains for 3 months resulted in a stool Firmicutes/Bacteroidetes ratio that seemed more similar to controls after the intervention (93). A double-blind, randomized, placebo-controlled trial of a Bifidobacterium probiotic in 33 children for 3 months found that those randomized to the probotic arm had a marginally greater increase in height percentile compared with the placebo group, without a difference in ongoing symptoms (94).

Administration of probiotics at the outset of CD diagnosis has been proposed as a potential therapeutic strategy and was tested in a pilot randomized, double-blind, placebo-controlled trial of 22 adults with elevated CD serologies who were still eating a gluten-containing diet and had not yet undergone duodenal biopsy. Compared with those randomized to placebo, those randomized to the probiotic Bifidobacterium natren (Life Start) had a greater improvement in gastrointestinal symptoms and lower levels of IgA antibodies to TTG and DGP (95).

Because many patients with CD have ongoing symptoms that are attributed to functional disorders such as irritable bowel syndrome (96), probiotics have been proposed to have a role in the treatment of these symptoms. In a randomized, double-blind, placebo-controlled trial of 109 adults with CD and irritable bowel syndrome-type symptoms, a combination probiotic consisting of Lactobacilli and Bifidobacteria for 6 weeks was superior to placebo in achieving the primary end point of an improvement of the irritable bowel syndrome severity scoring system, although quality of life scores did not improve (97).

Despite these promising pilot studies, there remain multiple uncertainties about the role of probiotics in the treatment of CD. The clinical significance of the symptom responses found in the above-cited trials was measured in the short term, and their durability is not certain. The implications of longer-term probiotic administration raise concerns for safety, particularly given the fact that probiotics marketed as supplements have a lax regulatory standard in the United States, with minimal safety data available before their introduction to the market. Indeed, there is concern that some probiotics on the market contain detectable gluten, despite being labeled gluten-free (98). The conventional wisdom of probiotics as a treatment of dysbiosis has also been questioned by a study that found that recovery from antibiotic-induced dysbiosis is actually delayed among individuals exposed to probotics (99).

Future research

- Do changes in the intestinal microbiome play a causal role in the development of CD?
- Does modification of the microbiome through orally administered probiotics result in improved clinical outcomes in CD?

Nutrition

5. In patients with newly diagnosed CD, what is the effect of GFD without oats on rates of clinical remission and mucosal healing compared with a gluten-free diet with oats?

Recommendation

5. We recommend consumption of gluten-free oats in the diet of those with CD. Gluten contamination of oats, variable toxicity in different varieties of oats, and the small risk for an immune reaction to the oat protein avenin require monitoring for oat tolerance (strong recommendation, moderate quality of evidence; dissent 0).

Key concepts

1. Oat consumption seems to be safe for most individuals with CD, but may be immunogenic in a subset of patients.
2. Heterogeneity in the tolerance of oats may be related to differences in the origin/harvesting and quantity of oats consumed.
3. Intervals for monitoring symptoms and serology after gluten-free oats are introduced into the diet are not known.

Background

The addition of pure/uncontaminated oats to a GFD in people with CD adds palatability, nutrition (soluble fiber, polyunsaturated oil, B vitamins, iron, thiamine), and laxation benefits. Variation in contamination by gluten-containing grains in different varieties of oats and their innate ability to trigger an immune reaction *in vitro* in some patients with CD confound interpretation of the literature on the safety of oats in patients following GFD (100).

Evidence and rationale

Given the distinct phylogenetic lineage of oats (*avenae*) from wheat, rye, and barley (*triticeae*), oats have been believed to be non-immunogenic in people with CD. However, there are conflicting reports as to the safety of oats in this population. Although some studies show good tolerance to oats, even at high amounts in adults and children (101–103), other studies show an increase in symptoms, intraepithelial lymphocytosis, villous atrophy on rechallenge, and avenin-specific T-cell inflammatory response (104–106). Whether studies that show intolerance to oats in the diet is due to increased fiber causing GI symptoms, contaminated oats, or an immunologic reaction to avenin in oats remains unknown. This has led to conflicting recommendations regarding the use of oats in a GFD in people with CD.

In a recent systematic review and meta-analysis (107) of the safety of oats in GFD in CD, 28 studies (661 patients, 6 randomized control trials, and 2 nonrandomized control trials) were included. Oat consumption in GFD for 12 months showed no effect on symptoms, histologic scores, or serologic test results in both adults and children with CD. The quality of evidence was deemed low because of the lack of type of origin and quantity of oats, variation in study design and time, small number of randomized controlled trials, and lack of information on compliance with GFD.

More recently, 2 studies have further supported the safety of pure/uncontaminated oats in people with CD following GFD. A large, cross-sectional study (108) of patients with CD from Finland reported that long-term consumption of oats was found to be safe and improved quality of life. Of the 869 subjects in the study, 82% ate oats with a median duration of 10 years. Those who ate oats when compared with those who did not eat oats showed no difference in dietary adherence to GFD, symptoms, positive EMA, histologic recovery after 1 year, malignancy, bone disease, or fractures. Those who consumed oats had better health scores. A double-blind,

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randomized, cross-over, placebo-controlled trial of the safety of oats in children with CD (109) reported that pure oat products are safe in the diet of children with CD. The study included 177 children (79 oats-placebo, 98 placebo-oats). The oat varieties used were "Irina and Potenza" *Avena sativa* that lack *in vitro* immune reaction in patients with CD and was double checked for contamination by using enzyme-linked immunosorbent assay testing. The oat treatment effect was not statistically significant for clinical symptoms, serologic results (anti-TTG, anti-avenin), or intestinal permeability changes.

Based on past and recent studies, Finnish pure oats and the *Avena sativa* oat varieties are safe when added to GFDs of children and adults with CD. Given the variety of oats with variable toxicity (110) and uncertainty as to whether oats stripped of gluten contamination during harvesting are considered safe for all people with CD, patients require monitoring for tolerance when pure/uncontaminated oats are added to GFD. This is in accordance with previous ACG 2013 CD guidelines to note that pure/uncontaminated oats can safely be ingested by people with CD, but that a small number may be intolerant of pure oats, and thus, they should be monitored for signs of clinical and serological relapse (1).

Future research

- Does an initial oats-avoidant strategy after diagnosis of CD result in improved symptoms and healing rates?
- What proportion of patients with CD mount an immune response to pure oats, and does this change over the course of the natural history of CD?
- What is the incremental benefit, in terms of symptoms, intestinal healing, and quality of life, of recommended pure/uncontaminated oats vs any oats?

Pneumococcal vaccine

6. For patients with CD, does the use of pneumococcal vaccine reduce the future risk of serious pneumococcal infection compared with no pneumococcal vaccine?

Recommendation

6. We suggest vaccination to prevent pneumococcal disease in patients with CD (conditional recommendation, low quality of evidence; dissent 0).

Key concepts

1. Vaccination against pneumococcal infection is safe and effective.
2. Vaccination is widely recommended for all adults older than 65 years and smokers aged 19–64 years or adults with certain underlying conditions.

Background

Vaccination plays a critical role to decrease the burden of pneumococcal infection. There are several available vaccines in the United States as follows: pneumococcal conjugated vaccine (PCV13, Prevnar13, Pfizer; PCV15, Vaxneuvance, Merck; and PCV20, Prevnar20, Wyeth Pharmaceuticals, LLC) and pneumococcal polysaccharide vaccine (PPSV23, Pneumovax, Merck). The Centers for Disease Control (CDC) recommend vaccination for all children younger than 2 years and all adults older than 65 years. Vaccination is also recommended for adults aged 19–64 years with certain underlying conditions (e.g., smoker and others). Pneumococcal vaccine is both safe and effective to decrease the burden of pneumococcal infection. The specific vaccination regimen depends on patient age, immunization record, and comorbidity following CDC recommendations. For example, in an adult patient with CD and functional asplenia (a common clinical association in CD), CDC recommends for those who have not previously received any pneumococcal vaccine or whose previous vaccination history is unknown to give 1 dose of PCV15 or PCV20: when PCV15 is used, this should be followed by a dose of PPSV23 at least 1 year later, and if PCV20 is used, a dose of PPSV23 is not indicated. For adult patients with CD and no other conditions with specific vaccination recommendation by CDC, we suggest to give 1 dose of PCV20 alone or 1 dose of PCV15 first and then consider to give 1 dose of PPSV23 at least 1 year later to maximize vaccine efficacy and protection. For complex vaccination scenarios, a vaccination clinic or infectious disease specialist consultation whenever available is reasonable.

Evidence and rationale

Adults with CD have a significantly increased risk of pneumococcal infections (sepsis, pneumonia) (111–113). In a population-based study using a health registry in Italy, children with CD were at increased risk of bacterial pneumonia compared with reference individuals, particularly before diagnosis, but pneumococcal infections were not significantly increased (114). The increased risk of pneumococcal infection is believed to be due to hyposplenism (frequently subclinical) found in approximately one-third of those with CD based on pitted red cell counting (115,116). In one small study, people with CD were capable of mounting antibody responses to a polyvalent pneumococcal vaccine, but it is uncertain whether those vaccinated had hyposplenism (117). In a recent systematic review and meta-analysis, CD was associated with an overall 2-fold increased risk of pneumococcal infection when compared with patients and general population (118).

Future research

- What is the effectiveness of the pneumococcal vaccine among patients with CD, and does this differ compared with the general population?
- Does a strategy of vaccination against pneumococcal disease among patients with CD younger than 65 years lead to reduced pneumococcal infection-related morbidity and mortality?
- What is the best vaccination regimen for patients with CD?

Screening

7. Should case finding vs mass screening be used to improve detection of CD in the general population?

Recommendation

7A. We recommend case finding to increase detection of CD in clinical practice (strong recommendation, low quality of evidence; dissent 0).

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7B. We recommend against mass screening for CD in the community (strong recommendation, low quality of evidence; dissent 0).

Key concepts

1. Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, abdominal pain, and bloating, should be tested for CD.
2. Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD.
3. Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested whether they show possible signs or symptoms or laboratory evidence of CD.
4. Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD.

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Background

The prevalence of CD is rising and detection is improving, but there is still a large burden of undetected disease. Testing symptomatic individuals with classical presentation (diarrhea and weight loss) is insufficient to detect most persons with CD. Strategies to increase detection of CD cases are controversial and include testing certain groups at increased risk (e.g., first-degree family members) called case finding and screening of asymptomatic individuals in the general population. Mass screening of asymptomatic individuals is not supported because CD does not fulfill some of the major World Health Organization criteria (Wilson and Junger) for mass screening, specifically the criteria that the natural history of the condition, including development of latent-to-declared disease, should be adequately understood and there should be an agreed policy on whom to treat as patients. Case finding is the current preferred strategy to increase detection of cases, although the pros and cons of this approach are still a matter of debate.

Table 4. Conditions to consider testing for celiac disease

CD common	CD less common but treatable
Symptomatic malabsorption	Pulmonary hemosiderosis
Diarrhea with weight loss	Male or female infertility
Chronic diarrhea with or without abdominal pain	Dyspepsia
Chronic iron deficiency and unexplained anemia	Amenorrhea
Metabolic bone disease and premature osteoporosis	Chronic fatigue
Postprandial bloating and gaseousness	Apparent malabsorption of thyroid replacement medication
Unexplained weight loss	Epilepsy or ataxia
Abnormal elevated liver enzymes	Constipation
Incidental discovery of villous atrophy endoscopically or histologically	Recurrent abdominal pain
Dermatitis herpetiformis	Chronic arthralgia
Peripheral neuropathy	"Brain fog"
Oral aphthous ulcers	Recurrent headache or migraine
Growth failure	
Discolored teeth or developmentally synchronous enamel loss	
Thyroid disease	
Irritable bowel syndrome	
Down and Turner syndromes	
Unexplained recurrent pancreatitis	

CD, celiac disease; GFD, gluten-free diet.
Conditions in which CD occurs more frequently than in the general population and for whom a GFD may be beneficial are listed on the left column. On the right column are conditions in which CD is a less common, but reversible, treatable cause.

Evidence and rationale

Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, irritable bowel syndrome, abdominal pain, and bloating, should be considered for testing for CD. CD is one of the most common causes of chronic malabsorption (119). This results from injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and consequential impaired absorption of micronutrients such as fat-soluble vitamins, iron, and potentially B_{12} and folic acid (3). In addition, the inflammation exacerbates symptoms of malabsorption by causing net secretion of fluid that can result in diarrhea. The failure of absorption of adequate calories leads to weight loss, and the maldigestion results in abdominal pain and bloating. These are common symptoms associated with CD (120).

In contrast to mass screening, case finding among high-prevalence groups may prove to be effective in clinical practice and perhaps lead to a positive cost-benefit ratio (121). However, recent evidence suggests that case finding is insufficient to detect most persons with undiagnosed CD at the population level (122). Patients with symptoms or syndromes for which CD is a treatable cause should be considered for testing for CD because this condition remains underdiagnosed in the United States (2) and may present in many ways. Currently, active case finding (serologic testing for CD in patients with symptoms or conditions closely associated with CD) is the favored strategy to increase detection of CD (1,123). Active case finding may increase detection of CD among patients with symptoms attending a primary care office, although this strategy is insufficient to detect most patients with CD (121). There is no consensus about which symptoms, laboratory abnormalities, and/or associated diseases require evaluation for CD. The frequency of CD in common clinical scenarios varies from modestly elevated, such as irritable bowel syndrome, to substantially elevated, such as unexplained iron deficiency anemia (124–126) (Table 4).

The complexity of deciding who to test could be appreciated using the example of dyspepsia. Prevalence of biopsy-proven CD in patients with dyspepsia is 1%, which is similar to the general population (127). Systematic screening for CD is not recommended because the prevalence of the disease is not higher than that in the general population. However, treatment of dyspepsia could be a clinical challenge. Endoscopy may be appropriate for patients who continue to have dyspepsia despite initial therapy, those who were 55 years and older, and/or those with alarm symptoms (128). Dyspepsia as a symptom of CD will readily respond to the GFD (129). Thus,

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evaluation for CD could be considered in patients with unexplained dyspepsia after initial investigation. In addition, obtaining duodenal biopsies in patients with dyspepsia who are undergoing upper endoscopy should be considered.

Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested for CD. The frequency of CD is substantially increased in patients who have a first-degree family member affected with CD (130). The precise risk is highest in monozygous twins, next HLA-matched siblings, siblings, and then finally, parents and children of patients with CD (18). A lower rate probably applies to second-degree relatives. Members of families who have more than 1 individual already identified with CD are at higher risk of CD, and recommendations for screening should extend to all other family members including second-degree relatives (131). The estimates of prevalence of CD in family members vary substantially with 1 large multicenter study in the United States, showing a rate as low as 5% in both first-degree relatives and second-degree relatives (18). Other studies, especially those that are community-based, show a rate that is substantially higher affecting up to 20% in siblings and 10% in other first-degree relatives (130). The clinical implications are that newly diagnosed patients with CD should inform their first-degree family members of the potential increased risk for CD and the recommendation for testing. In addition, healthcare providers should determine whether there is a family history of CD and, if so, consider screening the patient. Patients who are identified with CD through a screening process often have symptoms that may not have been previously explained. Others may have symptoms that were not considered abnormal until after they initiated a GFD (132). Screen-detected asymptomatic patients remain without symptoms after the onset of a GFD. Most patients with CD identified on the basis of screening reported dietary adherence and improvements in quality of life on the GFD (133). A small proportion of patients, however, report increased health-related anxiety after diagnosis (134). Satisfaction with the diagnosis was high (93%).

In patients with elevated serum liver enzymes, CD should be considered among the explanations for this condition (135). Abnormal liver blood tests, particularly elevations of alanine aminotransferase and aspartate aminotransferase, are commonly seen in clinical care, although the prevalence of clinically significant liver disease is low (136). Hypertransaminasemia in CD is often a subclinical finding that is gluten-dependent. Patients with unexplained elevation of liver enzymes should be assessed for CD. There are reasonable data to show that gluten-dependent hypertransaminasemia will normalize in most patients on a GFD. Rarely, CD can be associated with severe liver disease (137).

Patients with type I diabetes mellitus should be tested for CD if there are any suggestive symptoms or signs. There is evidence that CD is substantially more common in patients with type I diabetes than in the general White population. The estimates vary between 3% and 10% (138). In children, it has been suggested that yearly or every-other-year screening for CD be undertaken using serology. Patients with type I diabetes who are undergoing upper endoscopy should undergo duodenal biopsies to rule out CD if previous CD testing has not been undertaken.

Some evidence suggests that there is added disease burden to patients already struggling with the management of type I diabetes. In addition, there is good evidence that gastrointestinal symptoms present at diagnosis will respond to a GFD with overall improvement in quality of life related to GI symptoms. The impact of the identification and treatment of CD on the management of type I diabetes is mixed. Some data suggest an increase in absorption, leading to an increased insulin dose. Other data suggest improvement of diabetes controlled by reduction of hypoglycemic events, especially postprandially.

Future research

- What is the effect of screening for CD among asymptomatic average-risk and high-risk populations on quality of life and morbidity?
- What is the rate of seroconversion across the life course for individuals at increased risk of developing CD, and what is the optimal serologic screening interval?

Testing in Children

8. Are TTGA and DGP antibodies in combination more accurate in diagnosing CD in children younger than 2 years compared with TTG alone?

Recommendation

8A. We recommend the immunoglobulin IgA anti-TTG antibody (TTG-IgA) as the preferred single test for the detection of CD in children younger than 2 years who are not IgA-deficient (strong recommendation, moderate quality of evidence; dissent 0).

8B. We recommend that testing for CD in children with IgA deficiency be performed using IgG-based antibodies (DGP-IgG or TTG-IgG) (strong recommendation; moderate quality of evidence; dissent 0).

Key concepts

1. TTG-IgA and EMA-IgA are reported to be less accurate in children younger than 2 years.
2. Current guidelines recommend that testing for CD in children younger than 2 years include both TTG-IgA and DGP-IgG.

Background

Serology testing plays a central role for screening children at risk of CD including children younger than than 2 years. Controversy exists about the best serology approach for children younger than 2 years.

Evidence and rationale

Previous guidelines on the diagnosis and treatment of CD recommend that a combination of TTG and DGP tests be used to test for CD in children younger than 2 years (1,139). This recommendation was based on the belief that the TTG and EMA tests are less accurate in very young children. In support of this belief, a study published in 1991 (140) identified 32 of 277 children younger than 2 years with histological feature suggestive of CD who were negative for EMA but positive for antigliadin antibodies (AGA). However, CD was never confirmed beyond doubt with subsequent challenges and repeat biopsies in all these cases. A more recent study involving 251 IgA-sufficient children with CD younger than 18 months found antigliadin-IgA (AGA-IgA) antibodies to be more sensitive than either TTG-IgA or EMA-IgA (141). Overall in this age group, the AGA-IgA was elevated in 97% of cases while TTG-IgA and EMA-IgA were elevated in 83%. All children aged between 18 and 23.9 months had elevated AGA-IgA, and all but one had

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elevated TTG-IgA and EMA-IgA. All children who were 2 years older had elevated TTG-IgA, whereas only 90% had elevated AGA-IgA. Although these findings are noteworthy, the high rates of positive AGA antibodies in this study are at odds with many other studies that report these antibodies to be lower and more variable than TTG antibodies in general. For this reason, current guidelines do not recommend the use of AGA antibodies to test for CD (142).

More recent studies have questioned the validity of the recommendation to use combined tests in children younger than 2 years. In 7 studies involving a combined number of 639 children younger than 2 years with biopsy-confirmed CD, the TTG-IgA performed as well or better than the DGP-IgG in identifying children with the disease (143–149). In the largest single study involving 348 children younger than 2 years with CD, the sensitivity with the TTG-IgA was greater than that for DGP-IgG (100% vs 89%) (144). Based on these reports, it is no longer justified to combine the TTG-IgA with DGP-IgG when testing for CD in children younger than 2 years who are not IgA-deficient.

Future research

- What is the positive predictive value of isolated elevations of DGP antibodies (IgA or IgG) among children younger than 2 years who have normal total IgA levels?

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CONFLICTS OF INTEREST

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